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EXAMINER	
LE, EMILY M	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	09/630,319	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90,93,96,98-101,104,133-146 and 149-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90,93,96,98-101,104,133-146 and 149-151* is/are rejected.

7)☒ Claim(s) *143* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/02/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-89, 91-92, 94-95, 97, 102-103, 105-132 and 147-148 are cancelled. Claims 90, 93, 96, 98-101, 104, 133-146 and 149-151 are pending and under examination.

Claim Objections

2. Claim 143 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant case, claim 143, which depends on claim 96, which depends on independent claim 104, requires the CpG oligonucleotide to have a modified phosphate backbone; however, independent claim 104 has already set forth this requirement. Claim 104 requires the CpG oligonucleotide to have a modified phosphate backbone. Hence, it is found that claim 143 fails to further limit its parent claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 133, 135, 137 and 139 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In response to the new matter rejection issued, Applicant submits that support for the recitation "GCG trinucleotide" can be found in lines 10-12, column 8 of parent application no. 08/386063, which is now U.S. Patent no. 6,194,308, which is incorporated by reference.

Applicant's submission has been considered, however, it is not found persuasive. It should be noted that the rejection is not solely directed at the recitation "GCG trinucleotide", rather, it's the requirement that such trinucleotide be absent from the CpG oligonucleotide. With regard to Applicant's assertion that the requirement is incorporated by reference, it should be noted that the attempt to incorporate matter is not in compliance with 37 C.F.R. 1.57. Specifically, 37 C.F.R. 1.57 (f).

37 C.F.R. 1.57 (f) provides: Any insertion of material incorporated by reference into the specification or drawings of an application must be by way of an amendment to the specification or drawings. Such an amendment must be accompanied by a statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter.

Thus, until the incorporation by reference is perfected, the rejection is maintained. Additionally, it should be noted that U.S. Patent No. 6194308, as

identified by Applicant, is not related to the instant patent application. It is presumed that by 6194308, Applicant intends 6194388, which has a patent application no. of 08/386063.

The following is the rejection issued in the previous office action: Claim 133 is newly added claim. Claim 133 requires that a GCG trinucleotide is absent from the CpG oligonucleotide. Applicant notes that adequate written support for the limitation(s) recited in claim 133 can be found at lines 1-20 of page 16, line 24 at page 18, lines 28-29 of page 21 and lines 1-6 of page 22.

The Office has reviewed the cited passages and the entire specification. However, the Office cannot find support for the limitation(s) recited in newly added claim 133 at the passages cited or any part of the specification.

5. Claims 90, 93, 96, 98-101, 104, 133-146 and 149-151 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the office action, Applicant asserts that the claimed invention is enabled by the specification. To support Applicant's position, Applicant submits that the specification teaches the administration of a CpG oligonucleotide induces IFN-gamma. Applicant further submits that the specification shows production of antibody response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells, and monocytic cells (Examples 3-4, Example 11, Figure 6 and Figure

11), and production of IFN-gamma (Figure 15), as well as other cytokines. In all, Applicant submits that the specification asserts that the CpG oligonucleotides are useful in treating bacterial infection. Applicant further submits that the combination of immune parameters demonstrated with CpG oligonucleotides is sufficient to support Applicant's assertion that the CpG oligonucleotides would be useful in the treatment of bacterial infection.

Applicant's submission has been considered, however, it is not found persuasive. In the instant case, the Office has thoroughly reviewed Applicant's submission and the specification; however, it is found that none enables the skilled artisan to practice the claimed invention without an undue burden of experimentation. It is found that the specification does not contain any working examples directed at the administration of the CpG oligonucleotides to treat bacterial infection. All that is provided in the specification is the art recognized ability to stimulate an immune response and the induction of a Th1 immune response, which leads to the production of Th1 associated immune response, and the assertion of taking advantage of the immune stimulation induced b the CpG oligonucleotide to treat bacterial infection. In the instant case, the Office, Applicant and the art recognizes that the CpG oligonucleotides have immune stimulation activities, particularly the induction of Th1 immune response, however, such recognition is not sufficient to enable the skilled artisan to practice the claimed invention without an undue burden of experimentation. With regard to the assertion that because administration of the CpG oligonucleotide induces a Th1 immune response, it should be noted that the treatment of a variety of

diseases, including viral infection, is also contemplated on the same basis. The contemplated basis is that the disease can be treated with the induction of a Th1 immune response. In the instant case, it should be noted that the Office is not doubting the immune stimulation induced by CpG oligonucleotides. The issue here is how to harness that activity to render a therapeutic efficacy for use in the treatment of disease. The specification has not taught or shown the skilled artisan how to do harness the immune stimulation activity to render a therapeutic efficacy for use in the treatment of bacterial infection. The mere contemplation of treatment is not sufficient to demonstrate that the specification is enabling for the claimed invention. Applicant must provide guidance or direction on how to use the claimed invention without the imposition of an undue burden of experimentation on the skilled artisan. In the instant case, it is found that Applicant has not done so. Applicant has not provided a disclosure that would enable the skilled artisan to practice the claimed invention without an undue burden of experimentation. Hence, the claimed invention is not enabling.

In response to the enablement rejection, Applicant further submits that the claimed invention is not directed at the administration of cytokines or the use of Th1/Th2 immune response to treat bacterial infection.

Applicant's submission has been considered, however, it is not found persuasive. It should be noted that the enablement rejection is formulated based on the Wands factors, as a whole. It should further be noted that the claimed invention is directed at the treatment of bacterial infection. At the time the invention was made,

it is well known in the art that the CpG motif present in the oligonucleotide stimulates Th1 immune response, which induces the production of Th1 associated cytokines. In the instant case, while the claimed invention does not specifically recites the administration of a cytokine, it does relies on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease. Hence, the cytokine art was introduced in the enablement rejection to demonstrate the level of unpredictability and the quantity of experimentation that would be required of the skilled artisan attempting to practice the claimed invention.

In addition to above, Applicant submits several references to rebut the rejection that the references cited by the examiner as being sufficient to demonstrate that the unpredictability of the claimed invention.

Applicant's submission has been considered, however, it is not found persuasive. The examiner has carefully reviewed the references, and found that they do not establish that the claimed invention can be practiced without any unpredictability, which lends to the conclusion of undue burden of experimentation, and that the claimed invention is enabling at the time the invention was filed. In the instant case, all of the references, either directly or indirectly, established the use of CpG oligonucleotides to provide protective immunity against certain type of bacterial infection. None of the references cited demonstrate the administration CpG oligonucleotides to treat bacterial infection can be practiced without undue burden of experimentation. For example, Auricchio et al., Lee et al., Klinman, Verthelyi, Takeshita and Ishii; Klinman, Conover and Coban; Freidag et al.; Jeffermans et al.;

Raghavan et al.; Gomis et al.; Krieg et al., Elkins et al.; Weighardt et al.; Gursel et al.; and Klinman, Kamstrup, Verthelyi, I. Gursel, Ishii, Takeshita, and M. Gursel.; suggest taking advantage of the immunostimulatory activities accorded by CpG motif containing oligonucleotides to broadly stimulate the innate immune response to improve host resistance against infections agents, including bacteria. In the instant case, the Office appreciates the suggestion offered by these references, however, it remains that none of the references demonstrate the administration CpG oligonucleotides to treat bacterial infection can be practiced without undue burden of experimentation.

Additionally, contrary to Applicant's assertion, the references submitted do not demonstrate that the claimed invention can be predictability practiced by the skilled artisan. The references cited by Applicant further establish that much more experimentation, beyond the routine experimentation, would be necessary. In the case of Auricchio et al., Auricchio et al. establishes that years after the filing of the instant patent application, further characterization of the mechanism by which CpG indirectly promotes the killing of *M. tuberculosis* is needed [Last sentence of paragraph bridging pages 917-918; and last sentence of first full paragraph on page 918.] Additionally, while Klinman, Conover and Coban recognizes the protective immunity offered by the immune stimulation induced by CpG oligonucleotides, they also teach "[t]here are only a limited number of settings in which such short term protection might be of therapeutic benefit." [Paragraph bridging left and right column of page 5658.] In addition, it is important to note that Raghavan et al. notes that **CpG**

oligonucleotides have no direct antibacterial effect. [First full sentence, left column, page 7021.] Raghavan et al. teaches that the observed a reduction in the bacterial load of *H. pylori* in CpG oligonucleotide treated mice occurred concomitant with both up-regulation of RANTES production in the stomach and rapid recruitment of the immune cells to the gastric mucosa. [4th and 5th full sentence, left column, page 7021.] In the instant case, no such similar teachings can be found in Applicant's disclosure. Applicant has not contributed or attributed any particular type of regulation or immunoparameter that must be modulated in order to provide treatment for bacterial infections. Additionally, while Raghavan et al. does note a reduction in bacterial load, it should be noted that Raghavan et al. does not teach how to harness this observation to render a therapeutic treatment against bacterial infections.

Jeffermans et al. also notes that the protection conferred by CpG oligonucleotides, when administered prior to bacterial challenge, against M. tuberculosis is abrogated in IFN-gamma gene deficient mice. [Protection by CpG is abrogated in IFN-gamma gene-deficient mice section, page 149.] In the instant case, Jeffermans et al. establishes that the protective immunity against M. tuberculosis varies among different types of populations. In the case of Jeffermans et al., the populations are IFN-gamma gene deficient and non-deficient mice. With that established, it should be noted here that the claimed invention does not require that the subject being treated to have or be deficient of any particular gene or cytokine associated gene. It should further be noted that the specification does not contain

any guidance or direction establish the gene that the treatment must possess in order to benefit from the administration of a CpG oligonucleotide to treat against bacterial infection. Furthermore, it should be noted that the claimed invention is not directed at providing protective immunity against bacterial infection. The claimed invention is directed at treating bacterial infection in a subject in need thereof.

In addition to above, Jeffermans et al. also establishes that kinetic differences exist the protection conferred by the CpG oligonucleotides among different types of organisms. [Paragraph bridging pages 150-151.] Specifically, Jeffermans et al. notes that in infection with *Listeria monocytogenes*, at least 48 hours was required between the time of administration of the CpG oligonucleotide and the time of bacterial challenge with *Listeria monocytogenes*; whereas, in the case of *Leishmania major*, the protective effects of CpG oligonucleotides can be obtained when it is administration is delayed until 20 days after infection with *Leishmania major.*

The teachings of Jeffermans et al. are further echoed by Krieg et al. Krieg et al. further notes the essential role of IFN-gamma in mediating protection induced by CpG oligonucleotides. [2nd to last full paragraph, right column, page 2433.] As mentioned earlier, Krieg et al. establishes that the protective immunity against *Listeria monocytogenes* varies among different types of populations. In the case of Krieg et al., the populations are IFN-gamma gene deficient and non-deficient mice. With that established, it should be noted here that the claimed invention does not require that the subject being treated to have or be deficient of any particular gene or

cytokine associated gene. It should further be noted that the specification does not contain any guidance or direction establish the gene that the treatment must possess in order to benefit from the administration of a CpG oligonucleotide to treat against bacterial infection. Furthermore, it should be noted that the claimed invention is not directed at providing protective immunity against bacterial infection. The claimed invention is directed at treating bacterial infection in a subject in need thereof.

In addition to above, Krieg et al. also cautions against the administration of CpG oligonucleotides to induce excessive immune activation. Krieg et al. teaches that the while the data obtained suggest that immune activation resulting from exposure to a low to moderate amount of CpG oligonucleotide can be beneficial in increasing disease resistance, however, excessive immune activation is deleterious. [3rd full sentence, in first full paragraph, left column, page 2433.] In that regards, it should be noted that the claims does not specify an amount or a range of amount of CpG oligonucleotides to administer or not to administer. All that is provided in the claim is that the amount administered be sufficient to treat bacterial infection. However, upon inspection of the disclosure, the specification, no additional guidance can be found. The specification does not set forth any guidance relating to the amount of CpG oligonucleotides to administer to treat bacterial infection or not to administer.

Hayashi et al. recognizes the use of CpG oligonucleotides as an adjuvant to the treatment of *Mycobacterium avium* infection with the conventional antimycrobacterial agent clarithromycin.

In addition to Hayashi et al., Klinman, Verthelyi, Takeshita and Ishii also recognizes the use of CpG oligonucleotides as vaccine adjuvants. Klinman, Verthelyi, Takeshita and Ishii further puts it best when they write, "[T]he risks of using CpG ODN [oligonucleotides] or DNA vaccines to stimulate innate or adaptive immunity must be considered. These include the possibility of their (1) integrating into the host genome, increasing the risk of malignancy (by activating oncogenes or inactivating tumor suppressor genes, (2) inducing autoimmune disease (by triggering the recognition of transfected cells and/or the production of anti-DNA autoantibodies), (3) altering immune homeostasis (by skewing the balance between Th1, Th2 and proinflammatory cytokines), or (4) having direct toxic effects on the host." [First paragraph, Safety of Foreign DNA section, page 126.] In the instant case, the art clearly sets forth that use of CpG oligonucleotides in a subject at the time the invention was filed is still at its infancy stage. Furthermore, it is noted that Applicant hasn't set forth any guidance addressing any of the perceived risks with the administration of CpG oligonucleotides.

Gursel et al. establishes that years after the filing of the claimed invention, the art is still trying to harness the immunostimulatory activities of CpG oligonucleotides to render a therapeutic value. [First sentence, second full paragraph, left column, page 3324.] Gursel et al. further notes years after the filing of the claimed invention, CpG oligonucleotides show promise as immune adjuvants, anti-allergens and immunoprotective agents. [First sentence, abstract, page 3324] It should be noted here that Gursel et al. does not set forth the use of CpG oligonucleotides to treat

bacterial infection. Gursel et al. only notes its use as immune adjuvants, anti-allergens and immunoprotective agents. Thus, even years after the filing of the claimed invention, the art has yet to teach the therapeutic use of CpG oligonucleotides to treat bacterial infections.

Like Gursel et al., Klinman, Kamstrup, Verthelyi, I. Gursel, Ishii, Takeshita, and M. Gursel. recognize the use of CpG oligonucleotides as immune adjuvants, immune adjuvants, anti-allergens and immunoprotective agents. Klinman, Kamstrup, Verthelyi, I. Gursel, Ishii, Takeshita, and M. Gursel. does not establish the use of CpG oligonucleotides to treat bacterial infection. It should be noted here that the teachings of Klinman, Kamstrup, Verthelyi, I. Gursel, Ishii, Takeshita, and M. Gursel. are provided years after the filing of the claimed invention. Thus, even at the time Klinman, Kamstrup, Verthelyi, I. Gursel, Ishii, Takeshita, and M. Gursel. published, the art does not establish the use of CpG oligonucleotides to treat bacterial infections.

Elkins et al. notes that the bacterial determinants that stimulate either inflammatory or lymphocyte-dependent innate immune responses are poorly understood. [Last sentence, paragraph bridging left and right columns, page 2291.] In the instant case, Elkins et al. teachings further exemplifies the unpredictability that is encountered in the present art, treating bacterial infection. In the absence of a better understanding of the bacterial determinants that stimulate either inflammatory or lymphocyte-dependent innate immune responses, it would be difficult for the skilled artisan practicing the claimed invention to determine whether immune

stimulation induced by CpG oligonucleotide is sufficient to treat bacterial infection without blind experimentation.

While Elkins et al. finds that CpG oligonucleotides were able to provide protective immunity against infection with intracellular bacteria, Elkins et al. also finds that CpG oligonucleotides do not protect against infection with two extracellular bacterial pathogens. [Last sentence, paragraph bridging pages 2296-2297] Elkins et al. teaches that variability exists among different types of bacterium. In the instant case, it should be noted that the claims does not require the bacterial infection to be treated to be an intracellular or extracellular bacteria. The claimed invention encompasses both intracellular and extracellular bacterium. Overall, Elkins et al. exemplifies the unpredictability that is present in the art.

Applicant's submission has been considered, however, it is not found persuasive. As stated in the previous office action, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without an undue burden of experimentation. In the instant case, the specification is deficient in this domain. The specification does not teach those skilled in the art how to make and use the full scope of the claimed invention without an undue burden of experimentation. Furthermore, the deficiency of the specification cannot further be complemented by the teachings of the art. The art, at the time the invention was filed and at the present, clearly recognizes that the administration of CpG oligonucleotides to treat diseases, including bacterial infection, is not a trivial endeavor.

The following is the enablement rejection set forth in the previous office action:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

The broadest claim is directed to a process for treating bacterial infection in subjects with the administration of an oligonucleotide containing the CpG motif, wherein the oligonucleotide is stabilized.

Nature of the invention:

The nature of the claimed invention is directed at treating bacterial infections with the administration of an oligonucleotide that comprises the CpG motif in vertebrates diagnosed with said infection

Breadth of the claims:

The specification defines "subject" as a human or vertebrate animal including dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat and mouse. [Lines 27-28 of page 19 of the specification.] It should be noted that the specification is not limited humans, dogs, cats, horses, cows, pigs, sheeps, goats, chickens, rats and mice.

The specification also lists examples of infectious bacteria, which includes *Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps* (e.g., *M. tuberculosis, M. avium, M. Intracellulare, M. kansaii, M gordonae*), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter erogenes, Klebsiella pneuomiae, Pasturella multicoda, Bacteroides sp., Fusobacterium nucleatum, Sreptobacillus moniliformis, Treponema pallidium,*

Treponema pertenue, Leptospira, and *Actinomeyces israelli*. [Paragraph bridging pages 14-15 of the specification.] It should be noted that the specification is not limiting "bacteria" to only those listed at the cited passage.

Thus, in view of the disclosure, the breadth of the claims encompasses:

- **all vertebrate animals**
- **all bacterium**
- **all nucleic acid sequences that contains the CpG motif.**

Thus, the broadest breadth of the claimed invention encompasses the use of any nucleic acid sequences containing the CpG motif to treat infections caused by all bacteria in all vertebrate animals.

State of the Art:

The art acknowledges the importance of Th1 type immune response, which stimulates the production of Th1 associated cytokines, in contributing to the elimination of intracellular pathogens such as mycobacterium and virus. However, the art also teaches that:

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, **host response to exogenously administered cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state**.
- **Both Th1 and Th2 type of immune responses in necessary.** Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while

producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, **a tight control over where and when Th1 and Th2 immune responses happen is necessary**.[1]

- The **efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial.** For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection.[2]
- **Interleukin-12**, Th1 associated cytokine, induces different effector mechanisms that result in **either protection or exacerbation**.[3] Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice.
- **Interleukin 18,** a Th1 associated cytokine, is **responsible for the progression** of endotoxin-induced liver injury in mice primed with interleukin 18.[4]

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]

- **Interleukin 6 and interferon gamma**, both are Th1 associated cytokines, **augment the susceptibility** of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utlitising **HIV-1** strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1.[5]
- **Interleukin 2**, a Th1 associated cytokine, **increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies.** Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. [6]
- **Interferon gamma is ineffective against the virulent strain of Mycobacterium avium.** Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma.[7]

In all, the art amply recognizes the following **limitations**: **inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects**. The art notes that the efficacy of exogenous cytokines capable of potentiating normal host defense mechanisms may be curtailed in immunocompromised patients lacking the pertinent effector cells or containing

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[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

[7] Silva et al. Evaluation of IL-12 in immunotherapy and vaccine design in experimental Mycobacterium avium infections. The Journal of Immunology, 1998, Vo. 161, 5578-5585. [Last sentence, left column of page 5583, in particular.]

disease-related factors preventing lymphocyte activation. The art also notes that viral, bacterial and parasite adaptations to the presence of cytokines pose new problems and approaches based on cytokine intervention will have to take these factors into account.[8]

The CpG art teaches:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[9] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice.[10] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.
- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies.[11] The art frequently notes that the **specific nucleic acids**, purines and pyrimidines, surrounding the CpG motif, **influence both the level and type of immune stimulation**; the **spacings** between CpG motifs surrounding the CpG

[8] Masihi, K., paragraph bridging left and right columns of page 646, in particular.
[9] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]
[10] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]

motif **influence both the level and type of immune stimulation**; and the **type of cytokine stimulated** by oligonucleotides containing the CpG motif **varies from one oligonucleotide to the next**.[12, 13,14] The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence.[15]

- **In vitro observations do not accurately predict what happens in vivo**.[16]
- The **immunostimulatory activity of CpG oligonucleotides is species specific**. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.[17]
- The **immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another**.[18]

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[11] Krieg et al., paragraph that bridge pages 716-717, in particular.
[12] Mutwiri et al., last sentence of paragraph bridging pages 89-90.
[13] Ibid.
[14] Ibid, third to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[15] Krieg et al., paragraph that bridge pages 712-713, in particular.
[16] Mutwiri et al., second to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[17] Ibid, section 2.1, disclosed on page 90, in particular.
[18] Ibid, Table 1 on page 92, and first sentence in first full paragraph, left column of page 94, in particular.

- **Oligonucleotides containing the CpG motif increase the susceptibility to infection by *Candida albicans*.** [19] Ito et al. notes that although oligonucleotides containing the CpG motif promote Th1 immunity, the induction of IL-12 by the oligonucleotide increases infection by *Candida albicans* in mice, rather than protecting the mice from said infection.

Presence or absence of working examples:

The specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection.

All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif. For example, the working examples note that the immunostimulatory effect and the extent of the immunostimulatory effect induced by oligonucleotides containing the CpG motif varies with the length of the oligonucleotide containing CpG motif; the number of CpG motifs present in the oligonucleotide; the nucleic acid(s) that flanks the CpG motif; the presence or absence of a modified phosphate backbone; and the presence or absence of methylated cytosine...etc.

[19] Ito et al. CpG oligonucleotides increase the susceptibility of normal mice to infection by *Candida albicans*. Infection and Immunity, September 2005, Vol. 73, No. 9, 6154-6156. [See abstract of Ito et al.]

Additionally, the working examples set forth that the immunostimulatory effect of oligonucleotides containing the CpG motif varies from one oligonucleotide to the next.

In addition, the working examples also demonstrate that an oligonucleotide having the sequence set forth in SEQ ID NO: 10, which contains the CpG motif is capable of stimulating the production of interleukin-12 and interferon-gamma, both of which are Th-1 associated cytokines. The working examples also demonstrate that oligonucleotides having the sequence set forth in SEQ ID NOs: 115, 19, 15, 116 and 18, all of which contains the CpG motif are capable of stimulating the production of interleukin-6, a Th-1 associated cytokine in vitro; and oligonucleotides having the sequence set forth in SEQ ID NOs: 124 and 16, which also contain the CpG motif, are not capable of inducing interleukin-6 to the extent that is higher than the control, media. Additionally, the working example shows that an oligonucleotide having the sequence set forth in SEQ ID NO: 48, which also contains the CpG motif and a modified phosphate backbone are capable of inducing interleukin-6 production in vivo.

Lastly, the working examples demonstrates that oligonucleotides having the sequence set forth in SEQ ID NOs: 28-29, 101, 104-105, 7 and 3, all of which contains the CpG motif are capable of stimulating the production of interleukin-6, tumor necrosis factor-alpha, interferon-gamma, GM-CSF, and interleukin 12, Th-1 associated cytokines in human PMBC. And oligonucleotide having the sequence set forth in SEQ ID NO: 102, which contains a CpG motif, is capable of inducing just

interleukin-6, tumor necrosis factor-alpha, GM-CSF, and interleukin 12. The oligonucleotide having the sequence set forth in SEQ ID NO: 102 does not induce interferon-gamma production. Furthermore, the oligonucleotide having the sequence set forth in SEQ ID NO: 103, which contains a CpG motif, is capable of inducing just interleukin-6, interferon-gamma, tumor necrosis factor-alpha, and GM-CSF. The oligonucleotide having the sequence set forth in SEQ ID NO: 103 does not induce production of interleukin-12.

Amount of direction or guidance presented:

Beside a discussion of how various structural modification effects the immunostimulatory activity of oligonucleotides, as exemplified by the working examples, Applicant has not provided any direction or guidance directed at the use of any of the disclosed oligonucleotides containing CpG motif to treat bacterial infections in vertebrate.

All that is gathered from the specification is the contemplation of apply the generic immunostimulatory activity that is sometimes observed with oligonucleotides containing the CpG motif, to treat, prevent, or ameliorate bacterial infection. [Lines 5-15 of page 9.] It is also noted that the specification prefers nucleic acid sequences that stimulate cytokine production, particularly IL-l, IL-12, IFN-gamma, TNF-alpha, and GM-CSF. [Lines 24-30 of page 8.]

Predictability or unpredictability of the art:

As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable. The

level of immune stimulation varies from one oligonucleotide to the next. The type of cytokine stimulated by oligonucleotides containing CpG motif also varies from one oligonucleotide to the next.

In addition, as demonstrated by the cytokine art, the use of cytokines in the treatment of diseases is unpredictable. The art notes that the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines contribute to the spontaneity that is observed in treatment of infections with the cytokines.

Quantity of experimentation necessary:

In the instant, Applicant has not provided a nexus between the activities observed for various oligonucleotides containing the CpG motif and bacterial infections. Applicant has not provided any guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections. Applicant has provided any guidance pertaining to the type of activity that would need to be stimulated to provide effective treatment against bacterial infections. Applicant has not provided any guidance relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections. In all, Applicant has failed to provide any guidance relating the treatment of bacterial infection with oligonucleotides containing CpG motif.

In view of the complete absence of any guidance relating the claimed invention and the different immunostimulatory activities that is observed in the

specification, the skilled artisan cannot possible practice the claimed invention without extreme research and experimentations. **To practice the claimed invention, the skilled artisan would have to conduct extensive research and experimentation.**

Thus, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat bacterial infections; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan cannot possibly practice the claimed invention without an undue burden of research and experimentation.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982);

In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. In response to the double patenting rejections issued in the previous office action, and repeated below, Applicant deferred rebuttal until the indication of allowable subject matter. Thus, until the rejections are properly addressed, the rejections are maintained.

8. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/613916.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 19 of the conflicting patent application is directed at the treatment of mycobacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C.

The difference between the two claims is that claim 19 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the generic recitation CpG.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

The last difference between the two claims is that claim 19 of the conflicting patent application recites mycobacterial infections instead of bacterial infections. However, it is noted that mycobacterial infections is encompassed by the generic bacterial infections.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 10/224523.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 67 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the oligonucleotide is 14-100 residues in length.

The difference between the two claims is that claim 67 limits the length of the oligonucleotide to 14-100 residues in length. However, this length is encompassed by generic recitation oligonucleotide comprising the CpG; wherein the cited recitation does not limit the length of the oligonucleotide.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made

would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 10/787737.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 38 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C, and wherein the oligonucleotide is a stabilized oligonucleotide.

The difference between the two claims is that claim 38 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the recitation CpG.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/735592.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 30 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the oligonucleotide comprises the formula: 5'TCG$X_1X_3N_1$3'.

The difference between the two claims is that claim 30 limits the oligonucleotide to a particular structure. However, the structure that is recited in claim 30 is encompassed by the generic recitation oligonucleotide comprising the CpG motif.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was

made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 41 of copending Application No. 10/894682.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 41 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises unmethylated cytosine; the oligonucleotide comprises the formula: $5'X_1X_2CGX_3X_43'$; and the oligonucleotide is associated with a sterol, lipid, and a target cell specific binding ligand.

The difference between the two claims is that claim 41 limits the oligonucleotide to a particular structure. However, the structure that is recited in

claim 41 is encompassed by the generic recitation oligonucleotide comprising the CpG motif.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because stabilization of nucleic acid sequences are well known in the art.

The other difference between the two claims is that claim 41 of the conflicting patent application requires the oligonucleotide is associated with a sterol, lipid, and a target cell specific binding ligand. However, it should be noted that claim 104of the instant patent application does not exclude this element.

The last difference between the two claims is that claim 41 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the recitation CpG.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. A terminal disclaimer to U.S. Patent No. 6207646 is noted of record.

Conclusion

14. No claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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